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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,707	08/25/2006	Michitaka Sato	2006_1414A	3825

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EXAMINER	
LEESER, ERICH A	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,707	SATO ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,9-11,13,15,17-22 and 25* is/are rejected.

7)☒ Claim(s) *3-6,8,12,14,16, and 23-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

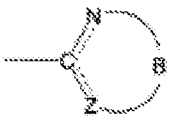
DETAILED ACTION

This action is in response to Applicant's Amendment in Response to Final Rejection dated October 27, 2008 in which Applicant amended claims 1 and 8. Claims 1-6 and 8-25 are pending and under examination.

Claim Rejections 35 U.S.C. § 112

Examiner previously rejected claims 1 and 17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Based on Applicant replacing the indefinite and ambiguous definition of Ar:



with definite moieties in claim 1, Examiner withdraws this rejection.

Claim Rejections 35 U.S.C. § 103

Examiner previously rejected claims 1-2, 7, 9-11, 13 and 15 under 35 U.S.C. § 103(a) as being unpatentable over Matsuoka, et al., Canada Patent No. 2431406.

Applicant argues that the use of the compounds of the reference and the use of the compounds of the instant invention are distinct and as such one skilled in the art at the time the invention was made would not be motivated to modify the compounds of the reference to arrive at the instant compounds. Applicant, however, fails to address the well-established case law that

the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 USPQ 137 (CCPA 1978) and *In re Lohr*, 137 USPQ 548, 549 (CCPA 1963). As such, Examiner maintains this rejection, however it is moot with regards to cancelled claim 7.

Examiner previously rejected claims 1, 6, 8-11, 13-15 and 23-25 under 35 U.S.C. § 103(a) as being unpatentable over Modica et al., *High Potent and Selective Arylpiperazine Derivatives as Ligands for the 5-HT1A Receptor*, Bioorganic & Medicinal Chemistry Letters, 10(10), 1089-1092 (2000) and claims 1, 6-7, 9-11, 13-16 and 23-25 under 35 U.S.C. § 103(a) as being unpatentable over Guccione, et al., *3D-QSAR Using "Multiconformer" Alignment: The Use of HASL in the Analysis of 5-HT1A Thienopyrimidinone Ligands,* Journal of Computer-Aided Molecular Design, 14(7), 647-657 (2000).

Because pyrimidine attached at the two position is not one of the moeity possibiliites of Ar, Examiner withdraws these rejections.

Claim Objections

Claims 3-6, 8, 12, 14, and 16, 18-21, and 23-25 are objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) The claim terms "5-HT_3 antagonistic agent" and "5-HT_{1A} agonistic agent" is unclear because it is not known by the rejected claims the structure of the compounds these terms are meant to describe. Does Applicant intend all such compounds in the art or just the ones claimed or disclosed in the specification. Either way, the claims need to be amended to make it clear to the reader the structure embodied by these ambiguous claim terms. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because while enabling for pyrimidine derivatives of formula (I) in which ring A is saturated, unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed, the specification does not enable the instant compounds to treat irritable bowel syndrome (IBS) with compounds of any other permutation of formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to pyrimidine derivatives or salts thereof which exhibit serotonin receptor subtype 3 ("5-HT_3") antagonistic activity and serotonin receptor subtype 1A ("5-HT_{1A}") agonistic activity concurrently which are used to treat irritable bowel syndrome by administering a therapeutically-effective amount of a compound of formula (I).

The state of the art:

The state of the art confirms that, for instance, 3-Amino-5,6,7,8-tetrahydro-2-{4-[4-(quinolin-2-yl)piperazin-1-yl]butyl}quinazolin-4(3H)-one is an effective treatment regimen for IBS. Tamaoki, et al., *Pharmacological Properties of 3-Amino-5,6,7,8-tetrahydro-2-{4-[4-(quinolin-2-yl)piperazin-1-yl]butyl}quinazolin-4(3H)-one (TZB-30878), a Novel Therapeutic Agent for Diarrhea-Predominant Irritable Bowel Syndrome (IBS) and Its Effects on an Experimental IBS Model*, The J. of Pharm. and Exper. Ther., Vol. 322, No. 3, 1315-23 (2007). However, this reference, nor any others found by Examiner, support the notion that pyrimidine derivatives of formula (I) of any other permutation besides those in which ring A is saturated,

unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed, are capable of effectively treating irritable bowel syndrome (IBS).

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize that pyrimidine derivatives of formula (I) of any other permutation besides those in which ring A is saturated, unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed, are capable of effectively treating irritable bowel syndrome (IBS).

Amount of guidance/working examples:

Applicant includes beginning on page 56 of the specification TABLE D entitled "Action of Compound of Present Invention on Defecation Under Stress", which begins with compound Example 4-1, 7-1, 7-6, and 7-20. Examiner makes a finding that the specification sufficiently teaches one of skill in the art how to use the claimed compounds to treat IBS where ring A is saturated, unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed, based on these four examples, but also makes the finding that the specification does not

enable the instant compounds to treat irritable bowel syndrome (IBS) with compounds of any other permutation of formula (I).

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to teach one of ordinary skill in the art how to use pyrimidine derivatives of formula (I) of any other permutation besides those in which ring A is saturated, unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed to effectively treat irritable bowel syndrome (IBS), one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to use Applicant's invention to treat irritable bowel syndrome with any other permutation of compounds of formula (I) besides those in which ring A is saturated, unsaturated or partially saturated carbohexyl group; X_1 is amino or methyl; X_1 is hydrogen; Y is a direct bond; n is 3; and Ar is the group represented by the second formula listed.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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